Fetal and Neonatal Hypoglycemia

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1.0 Introduction to General Topic

Although blood sugars have been measured in newborn infants since 1910, it was 1929 before Von Creveld reported blood sugar levels in low birth weight neonates were lower than those in term or older infants and children. Over the next 30 years, sporadic reports of newborn infants with profound, severe or recurrent hypoglycemia appeared including the classical reports of Hartmann and Jaudon in 1937, and McQuarrie in 1952. However, since 1959, with the recognition of transient symptomatic hypoglycemia in the small for gestational age (SGA) male infant, hypoglycemia has been recognized as a frequent problem in neonatal care (1). In addition, studies have provided a definition of normal and abnormal glucose values in blood in both full sized and low-birth weight infants, as well as a better understanding of glucose transport across the placenta and fetal physiology (2). In 1981, the modern era of understanding fetal and perinatal carbohydrate endocrinology and metabolism has arrived.

Thus, it is now known that size at birth and growth in utero depend upon fetal insulin secretion as well as availability of maternal substrates. Hypoglycemia occurs in 3 to 4 infants per 1000 live births, may be symptomatic or asymptomatic, and can produce severe sequelae, even death, if unrecognized or untreated.

A distinguished group of colleagues will present the current status of important aspects of hypoglyemica in the fetus and neonate. First: Professor Karlis Adamson, "In Utero" Events, from both a Theoretical and Clinical Point of View; then, Dr. Ingeborg Brandt, "The Frequency and Importance of Hypoglycemia in the Neonate"; third, Professor Petter Karlberg, "Metabolic Aspects of Care of Neonatal Hypoglycemia"; and last, myself.

2.0 Screening for Neonatal Hypoglycemia

In discussing a rapid simple and useful clinical approach to detect hypoglycemia, first, it is necessary to screen those infants at highest risk, utilizing either the Dextrostix® or Chemstrip® bG. Routine screening may be done at 1, 2, 4, 6, 12, 24 and 48 hours of age (1, 2). The high risk infants to be screened include all less than the 3rd or 10th (S.G.A.) or greater than the 95th (L.G.A.) percentile for weight, the smaller of discordant twins, infants of insulin dependent or gestational diabetic mothers, sévere erythroblastotics, isolated hepatomegaly or a positive family history of a sib with neonatal hypoglycemia or an unexplained neonatal death. Early screening is also indicated in infants with significant anoxia or perinatal distress (e.g. Apgar scores of < 5 at 1 minute) and in A.G.A. or L.G.A.

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babies either with exomphalos, macroglossia and gigantism (Beckwith-Weidman Syndrome) or with a microphallus and/or a congenital midline defect.

If the Dextrostix® or Chemstrip® are low and the infant asymptomatic, a blood or serum glucose is measured in the clinical chemistry laboratory. If significantly low (< 30 mg/dl in term, < 20 mg/dl LBW), an intravenous infusion of glucose (6 to 8 mg/kg/min) should be given to restore the glucose values to normal. This group represents about 50% of neonates with hypoglycemia (2).

If clinical manifestations such as tremors ("jitteriness"), limpness, episode of cyanosis, apnea, irregular respirations, an abnormal cry, irritability, apathy or seizures occur in any infant, screen the blood sugar at once. If low, obtain a blood sample for a laboratory glucose analysis while starting the intravenous glucose (ORAL GLUCOSE IS NOT THERAPY). If the laboratory glucose is low and the symptoms clear following intravenous glucose, the diagnosis of symptomatic hypoglycemia is verified. This group represents about 15% of neonatal hypoglycemia.

If symptoms persist or fail to clear completely even after correction of hypoglycemia, a search must be made for other underlying or associated pathology. This is critical since hypoglycemia may be secondary to central nervous system pathology (congenital defects, infections, hemorrhage or kernicterus), sepsis, hydrops fetalis, congenital heart disease, asphyxia, anoxia, adrenal hemorrhage, hypothyroidism, multiple congenital anomalies, neonatal tetany and iatrogenic factors i.e., cold injury, post-exchange transfusion, drugs to mother, or the abrupt cessation of hypertonic parenteral glucose. This is especially important in infants born to mothers taking narcotics or oral hypoglycemic agents or being given beta adrenergic agents to inhibit premature labor. These infants represent about 35% of neonatal hypoglycemics.

If the symptoms clear with intravenous glucose, but then tend to recur or if the low blood glucose values persist in the presence of adequate intravenous glucose (10-12 mg/kg/min) one must consider the possibility of hyperinsulinism, hypopituitarism or a metabolic defect. These represent the rare 1-2% of neonatal hypoglycemics who are L.G.A. or A.G.A. and especially at high risk. In these, the critical diagnostic blood sample must be obtained both before and after glucagon (3) for measurements of glucose ketones, FFA, lactate, alanine, uric acid, insulin, HGH, cortisol, glucagon, and T_4, T_3, TSH.

After these critical blood samples are obtained, a diagnostic-therapeutic trial is initiated and given sequentially without discontinuing the previous therapy. This includes: (1) increased rates of glucose administration to 12-14 mg/kg/min, (2)

Prednisone (2 mg/kg/day) or hydrocortisone (15 mg/kg/day), (3) HGH 1 u/day, (4) Diazoxide® 10-25 mg/kg/day, and (5) Surgery (2).

Hyperinsulinism - If the infant is large (60% are greater than 95th percentile); the hyperglycemic response to glucagon exceeds 40 mg/dl (3); the urine ketones are negative; and the blood ketones, F.F.A. and glucose are all low in the presence of a relatively elevated plasma insulin (> 12 μU/ml) (4), then beta cell pathology (hyperinsulinism) is the likely diagnosis.

If the infant is AGA or LGA (> 95th percentile in 25%), has a microphallus (males), midline defect, jaundice, hepatomegaly, low T_4, low growth hormone (HGH) and resistant hypoglycemia, congenital hypopituitarism is likely. Correction of hypoglycemia occurs after cortisol and/or HGH therapy is added. The hyperglycemic response to glucagon may be diminished or normal.

In a normal (AGA) or small (SGA) newborn, the presence of a metabolic acidosis, jaundice, hepatomegaly and elevated uric acid; reducing sugars, but no glucose, in the urine and ketonuria should suggest an inborn error in carbohydrate or amino acid metabolism. These include glycogen storage disease, galactosemia, FDPase deficiency, tyrosinemia, or maple syrup urine disease. A diminished (< 25 mg/dl) or absent hyperglycemic response to glucagon is characteristic of these infants.

The outcome in neonatal hypoglycemics depends upon proper diagnosis, early treatment, and the associated as well as the primary pathology. The prognosis for infants with severe recurrent or persistent hypoglycemia remains guarded. While life may be spared, the long term outcomes of infants following pancreatectomy, prolonged Diazoxide® therapy, and hormone replacement for congenital hypopituitarism are just being accumulated and await future analysis.

Bibliography

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